Protocol Title: Allogeneic Breast Protocol 2: Phase I Trial of T cell Exchange with Th2/Tc2 Cells for Allogeneic Stem Cell Transplantation After Reduced Intensity Conditioning for Metastatic Breast Cancer

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Study Objectives:

A) To determine the safety, as defined by the incidence of acute graft-versus-host disease, and feasibility of administering in vitro generated donor T cells of Th2/Tc2 phenotype to augment a T cell depleted allograft ("T cell exchange") after reduced-intensity conditioning.
B) To determine if the transplantation of a T cell depleted allograft augmented with Th2/Tc2 cells can result in a state of rapid complete donor chimerism after reduced-intensity conditioning regimen.
C) To determine whether the transplantation of a T cell depleted allograft augmented with Th2/Tc2 cells can result in clinical responses in patients with metastatic breast cancer.
D) To determine the progression-free and overall survival of metastatic breast cancer patients following allogeneic hematopoietic stem cell transplantation with this Th2/Tc2 approach.

Precis: Despite metastatic breast cancer's (MBC) responsiveness to available therapies, the prognosis for patients is poor and points to the need for new treatments of MBC. In Allogeneic Breast Protocol 1 we were able to demonstrate that allogeneic T cells could mediate a clinically relevant graft-versus-tumor (GVT) effect against MBC after a reduced intensity, T cell depleted allogeneic hematopoietic stem cell transplant (alloHSCT). Responses were not observed until the establishment of complete lymphoid chimerism, which was frequently delayed and required the use of planned donor lymphocyte infusions (DLI). DLI were associated with a significant incidence of graft-versus-host disease (GVHD). Establishment of complete donor lymphoid chimerism rapidly without significant GVHD would be a significant advance in allogeneic cellular therapy for metastatic breast cancer and other malignancies.

T cells of Th2/Tc2 phenotype have been shown in mouse transplant models to facilitate engraftment of HLA disparate allografts with significantly reduced GVHD as compared to unmanipulated T cell replete allografts. Th2/Tc2 cells also provide an anti-tumor effect through the perforin/granzyme pathway. Although the anti-tumor effects of Th2/Tc2 cells are reduced as compared to Tc1 cells alone or to a T cell replete allograft, both of which are associated with an increased incidence of GVHD, they still provide more anti-tumor activity than an allograft depleted of T cells. This Th2/Tc2 subset can be generated in humans. Based on these observations, we hypothesized that allogeneic Th2/Tc2 cells may represent a donor T cell population capable of facilitating allo-engraftment rapidly post-transplant with reduced GVHD. The earlier establishment of complete donor lymphoid chimerism will permit us to administer DLI specifically for anti-tumor activity. In addition, the anti-tumor activity of Th2/Tc2 cells should provide more early benefit than the T cell depleted allografts used in Allogeneic Breast Protocol 1. It is our belief that this approach will result in the rapid establishment of complete lymphoid engraftment without increased toxicity (*i.e.,* GVHD) and increase the response to allogeneic cellular therapy when the tumor is at a minimal disease state and before it has the opportunity to progress.

To test this hypothesis, patients with advanced MBC will receive donor Th2/Tc2 cells added to a T cell depleted allograft as part of an alloHSCT. Patients eligible for this protocol must have measurable, metastatic disease and an HLA matched sibling donor. Patients must have received treatment with a taxane, an anthracycline, a hormonal agent and/or Herceptin®, if the tumor expresses the respective receptors, and at least one treatment for metastatic disease that has not resulted in a complete response. Patients will receive induction (immune depleting) chemotherapy with the goal of reducing circulating CD4+ cell < 50/μl prior to proceeding to alloHSCT. Donors will initially have lymphocytes collected to generate the Th2/Tc2 product and then have blood stem cells collected following mobilization with filgrastim. The stem cell product will be T cell depleted, and the T cell dose will be adjusted to 1 x 10^5 CD3+ cells/kg. Patients will receive a reduced-intensity conditioning regimen consisting of fludarabine and cyclophosphamide. This will be followed by infusion of the T cell depleted allograft, which will be supplemented with Th2/Tc2 cells (*i.e.,* "T cell exchange"). Th2/Tc2 cells will be given at doses of 0.5 - 12.5 x 10^7 cells/kg in three patient cohorts in a phase I manner. Cyclosporine will be administered for 40 days to prevent GVHD and then discontinued to permit a full GVT effect. Patients may subsequently receive donor lymphocyte infusions at days +42, +70, +98 post-transplant to further potentiate a GVT effect.

Eligibility:

1. Patients with measurable stage IV breast cancer.
2. Patients must have received at least one prior chemotherapy regimen in the metastatic setting to which they had less than a complete response.
    a) Patients must have received prior therapy with a taxane and an anthracycline.
    b) Patients whose tumor expresses estrogen/progesterone receptors must have received at least one hormonal agent.
    c) Patients whose tumors express Her2-neu must have received trastuzumab (Herceptin®).
    d) Patients who have progressed after or did not achieve a complete response after autologous stem cell transplantation are eligible for this protocol.
    e) Patients who have received the above-mentioned agents in the adjuvant setting and subsequently relapsed are considered eligible for this protocol.
3. Patients 18 - 75 years of age.
4. Karnofsky performance status $\geq$ 60%.
5. Life expectancy > 6 months.
6. Left ventricular ejection fraction ≥45%, DLCO >50%, creatinine $\leq$ 1.5 mg/dl and a creatinine clearance $\geq$ 50 ml/min, direct bilirubin $\leq$ 2.5 mg/dl, SGOT < 4x top normal (hepatic laboratory values above these levels may be accepted if such elevations are thought to be due to liver involvement by malignancy).
7. Patients must not be infected with HIV, Hepatitis B, or Hepatitis C viruses. The high degree of immune suppression that will be used in this study may lead to the activation or progression of these viral illnesses.
8. Consenting first-degree relative matched at 6/6 HLA antigens.
9. Ability to give informed consent.

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